Acta Derm Venereol 2009; 89: 52–56

CLINICAL REPORT

Exogenous Histamine Aggravates Eczema in a Subgroup of Patients with Atopic Dermatitis

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Food and beverages may contain high amounts of histamine and thus may cause symptoms after ingestion. The aim of this study was to investigate the role of ingested histamine in atopic dermatitis. Patients with atopic dermatitis had to maintain a histamine-free diet for one week. Consecutively, double-blind, placebo-controlled provocations were performed with histamine-hydrochloride and placebo. The clinical outcome was assessed by determination of the SCORAD. Before and 30 min after each provocation blood was collected for measurement of plasma histamine levels and diamine oxidase activity. Thirty-six patients with atopic dermatitis completed the diet. Twelve of 36 showed a significant improvement of the SCORAD after one week of the diet. After provocation tests 11 of 36 showed aggravation of eczema. Plasma histamine was significantly higher in patients with atopic dermatitis compared with controls ($p < 0.001$), whereas diamine oxidase activity was similar in both groups. Our data indicate that ingestion of moderate or high amounts of histamine-hydrochloride may aggravate eczema in a subgroup of patients with atopic dermatitis. Plasma histamine and diamine oxidase activity were not associated with the clinical response to histamine. ***Key words: atopic dermatitis; diamine oxidase; histamine intolerance.***

(Accepted August 5, 2008.)

Acta Derm Venereol 2009; 89: 52–56.

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Atopic dermatitis (AD) is a chronic relapsing skin disease characterized by dryness of the skin, eczema and pruritus (1). Worldwide nearly 10–20% of children and 1–3% of adults are affected (2). The majority of affected individuals live in urban regions in industrialized countries (3). Hereditary disposition is a major cause of the disease (1). The severity of the symptoms is variable and can be triggered by various factors, including food allergens or by non-allergic food hypersensitivity reactions (4). Previous studies indicated that many adult patients report a food-related aggravation of skin symptoms (2, 5). In infancy and childhood, IgE-mediated food allergies are often relevant for worsening the eczema, whereas non-IgE-mediated reactions caused by food additives are less frequent (4). In up to 35% of children with AD aggravation of the eczema after the intake of food allergens such as milk, egg or wheat has been reported in severely affected children (6).

Histamine is a biogenic amine and the product of decarboxylation of the amino acid L-histidine. Food and beverages may contain biogenic amines in relevant amounts as a result of microbial contamination. Therefore, spoiled or fermented foods may contain high levels of biogenic amines (7). In particular, food items that undergo microbial ripening, such as cheese, salami, sauerkraut or red wine, may contain high levels of histamine. Histamine concentrations may vary widely, not only between different food varieties but also within single foods (7, 8).

Histamine intolerance belongs to the group of non-IgE-mediated hypersensitivity reactions and is a pharmacological food intolerance. There are currently no valid *in vitro* tests for proving histamine intolerance; thus, double-blind, placebo-controlled food challenge (DBPCFC) remains the gold standard for the diagnostic work-up of non-IgE-mediated food intolerances (9).

Biogenic amines are metabolized by specific enzymes (10). The histamine-degrading enzymes are diamine oxidase (DAO) and histamine methyltransferase (HMT). DAO is localized primarily in the jejunal mucosa and represents the first barrier for ingested histamine (8, 10, 11). The second enzyme, HMT, is localized mainly in the lung tissue and degrades the remaining histamine, which is passed into the bloodstream. Recently, it has been proposed that histamine intolerance is characterized by a deficiency or a reduced activity of DAO. Consequently, the ingestion of histamine, which is generally tolerated by healthy individuals, may more frequently lead to adverse reactions in histamine-intolerant patients (10, 11).

The possible impact of histamine on the local, but also systemic, immune response in the skin has been suggested by recent studies showing that histamine favours a Th1 response (12–14).

The aim of this study was to evaluate the role of ingested histamine as an aggravating factor in adult patients

 doi: 10.2340/00015555-0565
 ISSN 0001-5555

with AD. To investigate the histamine metabolism in this group in more detail the plasma histamine levels and DAO activity were determined and compared with those of a control group with healthy skin.

METHODS

Subjects

Subjects were recruited from the Allergy-Centre-Charité at the Department of Dermatology and Allergology, Charité. Patients with AD aged between 18 and 65 years were enrolled in this study. AD was diagnosed by the criteria of Hanifin & Rajka (15). A group of age- and sex-matched skin healthy volunteers served as controls. The study was approved by the local ethics committee and all participants gave informed consent before starting the study.

Study design

Patients with AD had to maintain a histamine-free diet for 2 weeks. The food restriction was based on a diet low in preservatives, colourings, antioxidants and other additives, as well as naturally occurring substances such as salicylates, benzoates or aromatic compounds, as described previously (4). In addition, foods with high amounts of histamine, such as fish, ripened cheese, smoked meat and alcohol were prohibited. No influence of a histamine-free diet on the skin of healthy controls was expected and, therefore, no diet was performed.

Patients and control subjects were not allowed to receive antihistamine medication throughout the study. The use of topical glucocorticoids was allowed on demand. During the second week oral provocations were performed. At intervals of 48 h three provocations were performed with capsules containing histamine-di-hydrochloride or placebo capsules containing mannite silicon dioxide. For titration two different dosages of histamine-di-hydrochloride were given, a lower dose with 0.75 kg^{-1} body weight and a higher dose with 1.5 mg kg^{-1} body weight according to the literature (16). Subjects were clinically observed for at least one hour after the challenges. Subjects with a severe immediate reaction after the first dose did not receive the second dose of histamine.

Skin status

At the beginning of the study, before and 48 h after each provocation the skin status of patients with AD was assessed by the same dermatologist using the Severity Scoring of Atopic Dermatitis (SCORAD) (17). As late-phase skin reactions arise within 24 and 48 h, an interval of 48 h was considered appropriate between the provocation tests, both for assessing positive skin reactions or for being sure no reaction occurred and the provocation can be continued. A clinically relevant improvement or aggravation of skin symptoms was defined as a change of ≥ 10 SCORAD points, respectively.

Blood samples

Blood samples for determining plasma histamine and serum DAO activity were drawn at the start of the study, before and 30 min after each histamine challenge.

Measurement of plasma histamine was performed by enzyme-linked immunoassay (ELISA) (Immunotech, Marseille, France) according to the manufacturer's recommendations. The expected reference value for healthy controls was < 10 nM. The DAO activity was determined by applying the C^{14}-putrescine method as described previously (18).

Statistical analysis

A two-factorial non-parametric analysis for longitudinal data (19) was performed to compare the time course of SCORAD, DAO and plasma histamine, respectively between the groups (i.e. patients with AD and controls).

The influence of diet or provocation within groups was evaluated by Wilcoxon-tests. p-values ≤ 0.05 were considered statistically significant. Calculations were performed with SPSS 11.0 (SPSS Inc, Chicago, IL, USA) and SAS (SAS Institute Inc, Cary NC, USA). Results are given as median (25–75% percentile) or as mean ± standard deviation (SD).

RESULTS

Subjects

Fifty-eight adult subjects with AD were recruited. Thirty-six completed the diet phase and underwent the DBPCFC (mean age 32 ± 1.4 years; 28 women, 8 men). The baseline SCORAD was 45 (38–49) points. Nineteen skin healthy individuals were included in the study as a control group (mean age 29 ± 1.3; 13 women, 6 men).

Improvement in skin status with histamine-free diet in patients with AD

The SCORAD decreased significantly after 7 days' diet in the AD group. The assessed median decline of SCORAD considering the whole group was –10% ($n = 36$; $p < 0.001$). During the challenge with both amounts of histamine (0.75 and 1.5 mg kg^{-1} body weight) an aggravation of skin symptoms was observed. No urticaria-like skin reactions were observed in any of the patients. Considering our criterion that a clinical relevant improvement of skin symptoms was defined as decrease of ≥ 10 SCORAD points, 12 of 36 patients with AD were considered as diet-responders because the SCORAD before diet was 47 (45–51) points and decreased significantly to 31 (31–35, $p = 0.002$) points after the diet. The histamine provocations in this group led to a significant increase in the SCORAD to 44 (33–49, $p = 0.037$) points after the first and to 53 (44–60, not significant) points after the second challenge. In the diet-non-responder group the SCORAD before and after diet was 42 (30–49 before, 34–47 after diet) points. After the first challenge, the SCORAD decreased to 37 (29–45) points and reached 39 (28–49) points after the second challenge, each change was not statistically significant (Fig. 1).

No significant change in the skin status was observed after placebo challenge in both subgroups (data not shown).

Systemic reactions

In some patients with AD, but also in healthy controls, the histamine provocation led to immediate systemic reactions. The severity of the symptoms varied from

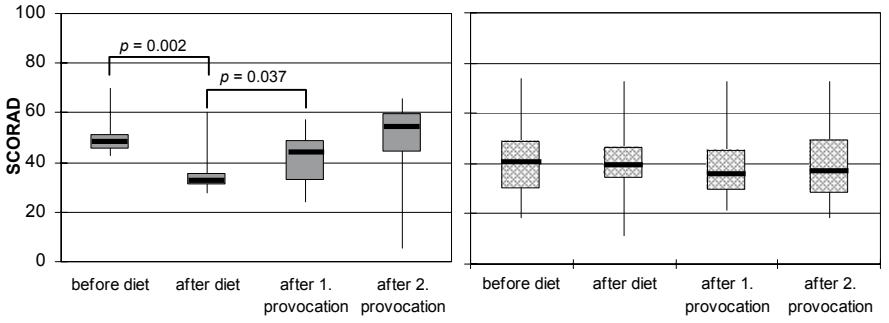

Fig. 1. SCORAD of patients with atopic dermatitis (AD). Classification in diet-responder (left, $n=12$), difference between before and after diet is –15.8 (–20.5 to –9.5), % change: –31.2 (–42.0 to –13.6); diet-non-responder (right, $n=24$), difference between before and after diet is –2.0 (–5.4 to –0.5), % change: –4.2 (–10.8 to –0.7). Median is shown as a black line, ends of the box represent 25% and 75% percentile, respectively. Outliers are not depicted.

mild (flush, headache, vertigo) to severe reactions (hypotension). Because of severity of the systemic reactions after the low-dose histamine provocation (0.75 mg kg^{-1} body weight) and the treatment with antihistamines, 2 patients with AD dropped out of the study. After the high dose histamine provocation (1.5 mg kg^{-1} body weight) 8 patients with AD had to stop the study because of hypotension. By contrast, within the control group only mild systemic reactions such as flush occurred, which did not require medical treatment.

Plasma histamine

The plasma histamine levels in subjects with AD were significantly higher compared with the control group ($p<0.001$; Fig. 2). At the beginning of the study the plasma histamine level in the patients with AD was 5.33 (3.95–9.44) nM and in the control group 3.06 (1.67–4.84) nM. In the patients with AD a significant increase in plasma histamine (median) was detected after the first histamine provocation from 5.39 to 6.91 nM ($p=0.002$) and after the second one from 6.10 to 8.57 nM ($p=0.029$), whereas the placebo provocation (3. provocation, Fig. 2) did not result in significant altered plasma histamine levels. In the control group only the high-dose provocation with histamine (2. provocation, Fig. 2) led to a significant increase in plasma histamine levels from 3.44 to 5.38 nM ($p=0.004$).

Significant differences in plasma histamine levels were observed neither for diet-responders vs. diet-non-responders nor for subjects with eczematous skin reaction vs. individuals without skin reaction (data not shown).

Diamine oxidase activity

The overall DAO activity did not differ significantly between patients with AD compared with controls. At the beginning of the study the DAO activity of the patients with AD was 10 (5.8–18.7) U ml^{-1} and of the healthy control group 14 (12.1–19.1) U ml^{-1}. Analysing the course of DAO activity within each group during the whole study period, there was no statistically significant change in the AD group detectable. In the control group a significant decrease of DAO activity (13 (1.5–33.1) before to 11 (4.2–30.4) after the provocation; $n=19$; $p=0.043$) was detected after the high histamine intake (1.5 mg kg^{-1} body weight). The diet-responder group also showed a significant decrease in DAO activity after the high histamine dose provocation ($p=0.036$, data not shown). Considering gender, no statistically significant differences between women and men regarding the analysed parameters (SCORAD, plasma histamine levels or DAO activity) were observed (data not shown).

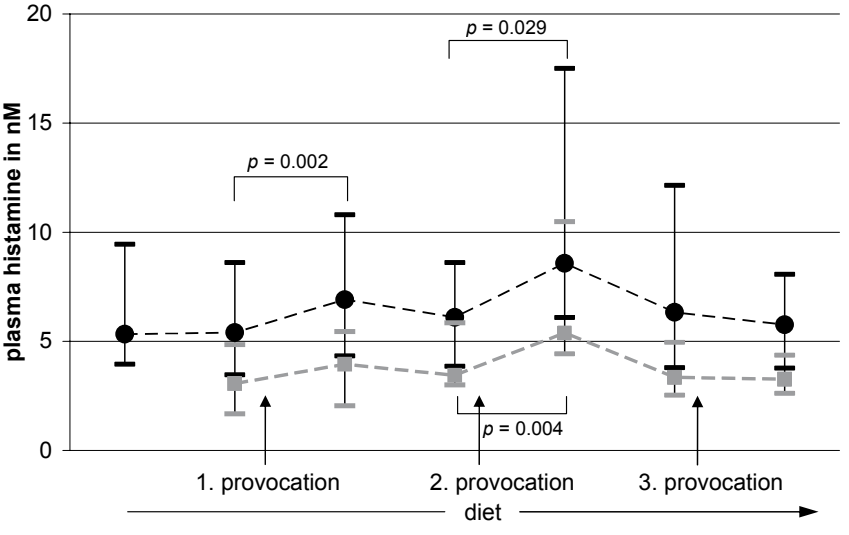

Fig. 2. Plasma histamine levels in both study groups during the study period (median; 25% and 75% percentile). Dots indicate patients with atopic dermatitis (AD) ($n=36$), squares indicate controls ($n=19$). Arrows indicate time-point of provocation with histamine-di-hydrochloride (1. provocation = 0.75 and 2. provocation = 1.5 mg kg^{-1} body weight) and placebo (3. provocation). Patients with AD showed a significant increase in plasma histamine after the first and second provocation ($p=0.002$ and $p=0.029$, respectively). In controls only the high-dose provocation (2. provocation) led to a significant increase ($p=0.004$).

DISCUSSION

Non-IgE-mediated hypersensitivity reactions against food have previously been shown to play a role in the skin status of adult patients with AD (4). The correlation between the ingestion of food rich in biogenic amines, e.g. histamine, and non-IgE mediated food hypersensitivity reactions is still not clarified in detail. Currently, no scientific background for dietary recommendations, concerning biogenic amines in patients with AD exists (20).

In this study the impact of a defined histamine intake on the skin status of adult patients with AD was examined. From the 58 initially recruited patients with AD, 36 completed the study. The main reason for this high drop-out rate was the fact that the patients were unable to adhere to the histamine-free diet. It is known that any kind of elimination diet can be difficult to manage in everyday life. Suspected food hypersensitivity was not among the main inclusion criteria. Therefore, for some patients it might have been difficult to maintain a histamine-free diet. However, our results indicate that approximately 30% of adult patients with AD benefit from a histamine-free diet with an improvement in the eczema. Correspondingly, we divided the study population into a diet-responder and a diet-non-responder group. In total, 81% of patients with AD had elevated total IgE and multiple type-I-sensitizations and 19% had normal IgE-levels. The observed distribution corresponds with the frequency stated in the literature regarding extrinsic (70–80%) and intrinsic (20–30%) AD among the adult patients with AD (21). The type of AD was independent of the response to the histamine-free diet. We identified diet-responders and non-diet-responders in both types of AD (data not shown).

The intake of high amounts of histamine caused a clinical relevant worsening of eczema in the diet-responder group only. This data strengthens recent observations that histamine has immune-modulating functions and may promote T-cell dependent cytokine production (12, 13). Histamine has diverse effects on Th1 and Th2 cells, as shown previously (12). Whether differences in histamine receptor (HR) expression in the skin of patients with AD might be relevant is currently under investigation. However, our clinical observations suggest a role of histamine in the inflammatory process of the skin, either directly or indirectly. As histamine receptors H1R and H2R and recently H4R are observed on monocyte-derived dendritic cells, these may also be activated by histamine (14, 22).

The elevated plasma histamine levels in patients with AD in comparison to the control subjects confirm the assumption that histamine is an important mediator for eczema aggravation in AD. Thus, antihistamines may support the treatment of AD. For example, the study by Kawashima et al. (23) showed that the daily intake of 120 mg fexofenadine, a non-sedating H1R antagonist, significantly decreased pruritus and had a positive effect on the skin status in patients with AD. However, other well-conducted studies suggest inefficiency of antihistamines in the therapy of AD (24). This implicates that higher dose of antihistamines may be required to achieve sufficient efficacy or other HR as H1R are needed to be targeted to achieve clinical efficacy. On the other hand, it should also be considered that the inflammation in the skin and pruritus in particular are not exclusively dependent on histamine. Other mediators like interleukin (IL)-31 (25) or neuropeptides like substance P (26) can promote the inflammatory process and mediate itch as well. Such factors may also be responsible for the observation that only a subgroup of patients with AD benefit from a histamine-free diet.

With our study design no decrease in plasma histamine was detected in the diet-responder group. Perhaps a longer diet phase would have been required to achieve this. On the other hand, one can speculate that the diet phase was sufficient to reduce histamine levels in the skin. This hypothesis can be addressed, e.g. by microdialysis of the skin before and after the diet phase.

Earlier studies by Wantke et al. (18) have shown that antihistamines such as diphenhydramine can enhance DAO activity *in vitro*. It is not known whether DAO activity is important in the pathogenesis of AD. If this is the case, it would be an additional therapeutic approach. Following this hypothesis one can speculate whether the intake of DAO as a drug will result in a reduction in plasma histamine levels and will therefore be of therapeutic interest for patients with AD. However, this needs to be confirmed by prospective clinical trials.

The relation between plasma histamine and DAO activity is not yet clarified. We observed increased plasma histamine levels in severely affected patients with AD compared with the control group and compared with the patients with AD with mild eczema. Whether this elevated plasma histamine level in patients with AD is a result of decreased histamine metabolism or whether it indicates an ongoing histamine release via IgE-mediated reactions, or both, needs to be clarified in future studies.

Systemic reactions, ranging from mild to severe, were observed in both study groups. Our data shows that within the healthy control group only mild symptoms such as flush occurred, which did not last longer than 5–10 min. In contrast, 10 patients with AD had severe reactions after histamine intake, such as hypotension. All these individuals with systemic reactions after histamine provocation had no decreased DAO activity, indicating that there is no direct correlation between DAO levels and clinical hypersensitivity to histamine. A recent study suggested a significant correlation of reduced DAO activity and severity of eczema in patients with AD (27). In contrast, we did not find significantly lower DAO levels in patients with AD, as measured at 7 time-points, compared with healthy controls. However, a significant correlation between plasma histamine levels and severity of eczema was observed.

Whether and to what extent other mechanisms of histamine degradation are also important, e.g. activity of HMT, the second histamine degrading enzyme is not exactly known (28, 29).

Finally, a selection bias has to be anticipated, since patients who suffer from food hypersensitivity were more likely to complete the study. Additionally, the sex distribution was not equal because we performed a random inclusion without stratification. Only 8 men vs. 28 women were randomized. Thirdly, the ratio of women to men among the AD and the control group differ (AD group = 3.5; control group = 2.1).

In summary, we conclude from our data that high amounts of ingested histamine may aggravate eczema in approximately 30% of patients with AD. Because no direct correlation between DAO activity, plasma histamine levels and skin reactions were observed, these parameters are not predictive to indicate the presence of either histamine intolerance or a role of histamine for an aggravation of eczema in AD.

ACKNOWLEDGEMENTS

We thank Sven Guhl, Susanne Lescau, Karin Forschner and Margit Focke for their excellent technical assistance and their helpful cooperation.

The authors declare no conflict of interest.

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Evidence for a reduced histamine degradation capacity in a subgroup of patients with atopic eczema

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Background: A diminished histamine degradation based on a reduced diaminoxidase activity is suspected as a reason for non–IgE-mediated food intolerance caused by histamine. Atopic eczema (AE) is often complicated by relapses triggered by IgE-mediated allergy to different kinds of food. However, in a subgroup of patients with AE, allergy testing proves negative, although these patients report a coherence of food intake and worsening of AE and describe symptoms that are very similar to histamine intolerance (HIT).
Objectives: It was the aim of our study to evaluate symptoms of HIT in combination with diaminoxidase levels in a total of 360 individuals consisting of patients with AE (n = 162) in comparison with patients with HIT (n = 124) without AE and healthy control volunteers (n = 85).
Methods: Histamine plasma level was determined with an ELISA and diaminoxidase serum activity with the help of radio extraction assays using [3H]-labeled putrescine-dihydrochloride as a substrate. Detailed clinical evaluations of characteristic features of AE and HIT were performed.
Results: Reduced diaminoxidase serum levels leading to occurrence of HIT symptoms like chronic headache, dysmenorrhea, flushing, gastrointestinal symptoms, and intolerance of histamine-rich food and alcohol were significantly more common in patients with AE than in controls. Reduction of both symptoms of HIT and Severity Scoring of Atopic Dermatitis could be achieved by a histamine-free diet in the subgroup of patients with AE and low diaminoxidase serum levels.
Conclusion: Higher histamine plasma levels combined with a reduced histamine degradation capacity might influence the clinical course of a subgroup of patients with AE.
Clinical implications: As HIT emerges in a subgroup of patients with AE, a detailed anamnestic evaluation of food intolerance and HIT symptoms complemented by an allergological screening for food allergy, a diet diary, and, in confirmed suspicion of HIT, measurement of diaminoxidase activity and a histamine-free diet should be undertaken. (J Allergy Clin Immunol 2006;117:1106-12.)

Key words: *Atopic eczema, histamine, diaminoxidase, food intolerance, allergy*

Numerous undesirable reactions to alcoholic beverages, food, drugs, and other substances are characterized by allergy-like signs and symptoms such as chronic headache, diarrhea, vomiting, flush, urticaria, asthma, and others. Histamine and other biogenic amines are present to varying degrees in many foods. Histamine content increases by maturing and fermentation processes.[1,2] The main enzyme for metabolism of ingested histamine is diaminoxidase,[2-6] a copper-containing amino oxidase[7-10] with a molecular mass of 90 kd. It has been proposed that diaminoxidase as a secretory protein[11,12] might be responsible for scavenging extracellular histamine after mediator release. Conversely, histamine N-methyltransferase (HNMT), the second important enzyme inactivating histamine, is a cytosolic protein[13] that can convert histamine only in the intracellular space of cells.[14,15]

A diminished histamine degradation based on a reduced diaminoxidase activity is suspected as a reason for non–IgE-mediated food intolerance caused by histamine.[16-23] Histamine is a potent mediator of numerous biological reactions such as the degranulation of mast cells in consequence of IgE-mediated allergen challenge of these cells in several allergic diseases. Via different histamine receptors, histamine causes smooth muscle contraction, vasodilatation, extravasation of plasma from capillaries, and stimulation of gastric acid secretion and nociceptive nerves. Together, these mechanisms are responsible for the typical symptoms such as diarrhea, headache,[24] hypotension, arrhythmias, urticaria,[25-27] pruritus, flushing, and even asthma[16,22,28] after ingestion of histamine-rich food,[16] alcohol,[21,22,29] or drugs releasing histamine or blocking diaminoxidase.[18,28,30] Symptoms can be reduced with a histamine-free diet[20,31,32] or can be eliminated by H1-blocker premedication.[16,17,21,24]

Atopic eczema (AE) is a chronic inflammatory skin disease that shows a wide variety of clinical pictures and that is often complicated by relapses of AE caused by different kinds of food. In a high number of patients with AE, IgE-mediated food hypersensitivities can be confirmed by skin prick tests, analysis of allergen specific IgE against food allergens in the sera, atopy patch tests, or oral allergen challenge.[33,34] However, in a subgroup of patients with

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Supported by grants from the Deutsche Forschungsgemeinschaft (DFG NO454/1-4 and DFG NO454/2-3) and a BONFOR grant of the University of Bonn. Dr Novak is supported by a Heisenberg-Fellowship, DFG NO454/3-1.
Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.
Received for publication July 30, 2005; revised November 15, 2005; accepted for publication November 29, 2005.
Available online February 8, 2006.

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0091-6749/$32.00

doi:10.1016/j.jaci.2005.11.041

Abbreviations used
AE: Atopic eczema
FA: Food allergy
HIT: Histamine intolerance
HNMT: Histamine-N-methyltransferase
SCORAD: Severity Scoring of Atopic Dermatitis

AE, allergy testing proves negative, or the allergy-like symptoms and the type of sensitizations present in the individual patient cannot be linked with the type of food and beverages ingested.[35] Nevertheless, these patients report a coherence of food intake and worsening of AE and describe symptoms that resemble histamine intolerance (HIT).

Therefore, it was the aim of our study to evaluate whether HIT might be of relevance in a subgroup of patients with AE.

METHODS

Characterization of patients

A total of 162 adult AE[36] patients (age range, 14-86 years; average age, 31.42 ± 12.95 years; 106 female and 56 male) from the Department of Dermatology in Bonn, Germany, were analyzed regarding atopic status, and the severity of the disease was evaluated according to the Diepgen score,[37] the criteria of Bos,[38] the criteria of Hanifin and Rajka,[39] and the Severity Scoring of Atopic Dermatitis (SCORAD) system,[40] respectively. In parallel, typical clinical symptoms of HIT and a history of food intolerance were evaluated with a standard questionnaire. Food intolerance was defined as non–IgE-mediated reaction to histamine-rich food such as worsening or development of the aforementioned HIT symptoms or worsening of pruritus and eczema. For control purposes, 85 healthy donors without any history of HIT or AE (age range, 17-63 years; average age, 30.58 ± 10.31 years; 57 female and 28 male) and 124 donors with a clinical manifestation of HIT without AE (age range, 6-75 years; average age, 48.43 ± 15.21 years; 101 female and 23 male) were investigated. The diagnosis of HIT was defined as patients reporting 2 or more positive symptoms of HIT and an improvement of these symptoms as a result of a histamine-free diet. In parallel, diaminoxidase serum levels were evaluated in these patients. The protocol was approved by the local ethics committee.

Analysis of total serum IgE, allergen-specific IgE

Total serum IgE and allergen specific IgE against *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), birch pollen, Timothy grass pollen, cat dander, hazelnut, peanut, milk, egg, apple, *Aspergillus fumigatus*, *Candida albicans*, *Malassezia sympodialis*, and codfish in the sera were analyzed with an Immulite 2000 System (DPC Biermann, Bad Nauheim, Germany).

Quantitative determination of the diaminoxidase activity in serum

Diaminoxidase activity assay was performed according to the manufacturer's instructions (Immunodiagnostik AG, Bensheim, Germany). Briefly, serum samples were collected and centrifuged for 10 minutes at approximately 1000*g* and stored at −20°C. Diaminoxidase activity was determined quantitating the reaction product, and radiolabeled putrescine-dihydrochloride was used as substrate. The resulting 3H-thymidine-labeled pyrolline was extracted selectively from the matrix by a liquid extraction step. Finally, radioactivity was determined by a β-counter. The signal detected was directly proportional to the activity of diaminoxidase in the sample, which was calculated according to a standard curve.[41] According to the literature, diaminoxidase activity lower than 3 U/mL was considered decreased.[23]

Analysis of laboratory parameters

Plasma level of histamine was evaluated according to the manufacturer's instructions (Immunotech, Marseille, France).

The amount of eosinophilic cationic protein in the sera of the volunteers was evaluated with the Immulite 2000 System. Serum tryptase levels were determined with the UniCAP System (Pharmacia Diagnostics, Uppsala, Sweden).

Zinc levels in the sera of the patients were measured quantitatively by atomic absorbtion spectrometry after deproteination of the serum with acetic acid (Bioscientia, Ingelheim, Germany). Copper serum levels and vitamin B_6 plasma levels were determined according to the manufacturer's instructions (copper: HITADO Diagnostic Systems, Möhnesee Delecke, Germany; vitamin B_6: Immunodiagnostik AG, Bensheim, Germany).

Conduction of histamine-free diet in a subgroup of patients with AE and HIT

A subgroup of patients with AE and HIT and low diaminoxidase activity (n = 17) underwent intensive nutritional consulting and histamine-free diet combined with intake of oral antihistamines once a day over a period of 2 weeks. Alcohol and long matured or fermented food rich in histamine like old cheese, fish, hard cured sausages, bread products containing yeast, vegetables like spinach, tomatoes, histamine-liberating fruits like citrus fruits, and other histamine-rich food had to be strictly avoided. In parallel, symptoms of HIT and AE were documented with the help of a standardized diet diary. At the beginning and after 2 weeks of the histamine-free diet, the objective and subjective SCORAD was evaluated in each patient. Serum diaminoxidase activity was compared in 5 patients before and after diet.

Statistical analysis

Statistical analysis using the Wilcoxon test was performed with SPSS 12.0 for Windows (SPSS, Chicago, Ill). Calculated values shown were means ± SDs. In addition, the frequencies of the different parameters between the different groups were compared by using the χ^2 test and the Mann-Whitney *U* test.

RESULTS

Symptoms of HIT occur in a subgroup of patients with AE

To analyze the frequency of HIT in patients with AE, we evaluated the occurrence of classical symptoms of HIT in patients with AE selected randomly by a standard questionnaire.

Symptoms of HIT such as chronic headache ($P = .003$; $\chi^2 = 8.556$), premenstrual headache and dysmenorrhea ($P = .002$; $\chi^2 = 9.295$), flushing ($P < .001$; $\chi^2 = 24.67$), gastrointestinal symptoms such as diarrhea, cramps, and meteorism ($P < .001$; $\chi^2 = 38.89$) and intolerance of food rich in or releasing histamine ($P < .001$; $\chi^2 = 51.85$) and alcohol ($P < .001$; $\chi^2 = 18.485$) occurred significantly more often in patients with AE than in controls

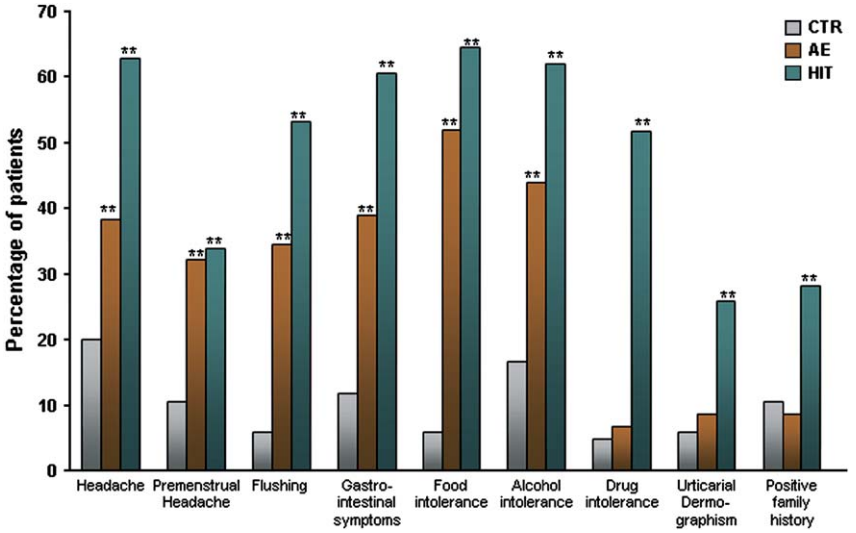

FIG 1. Symptoms for HIT are high in patients with AE. Symptoms of HIT in patients with a suspected HIT without AE (*HIT*; n = 124), patients with AE (n = 162), and healthy controls (*CTR*; n = 85) are shown. The percentage of patients showing symptoms and or low diaminoxidase activity is depicted on the *x-axis*. $^{**}P < .01$ in comparison with healthy control group (CTR).

TABLE I. Low and normal diaminoxidase (DAO) activity in serum from patients with suspected HIT, patients with AE, and a healthy control group (CTR)

	Total number	Low DAO		Normal DAO			
	n	n	%	n	%	*P* value*	χ^2
CTR	85	0	0	85	100		
AE	162	31	19.14	131	80.86	<.001	18.6
HIT	124	25	20.16	99	79.84	<.001	19.466

*Statistical analysis has been performed with the χ^2 test.

(Fig 1). Drug intolerance ($P = .52$; $\chi^2 = 0.425$), urticarial dermographism ($P = .44$; $\chi^2 = 0.588$), and a positive family history regarding HIT symptoms ($P = .62$; $\chi^2 = 0.25$) did not differ significantly from the control group (Fig 1).

Reduced diaminoxidase serum level in a high number of patients with AE

To evaluate the histamine degradation capacity of patients with AE, we performed analyses in which we measured the diaminoxidase activity in the sera of patients with AE in comparison with healthy volunteers and patients with HIT but without AE. We observed both a significantly lower mean of the diaminoxidase activity in patients with AE ($P < .001$) compared with controls and a higher total number of patients with AE displaying a reduced diaminoxidase serum level in comparison with healthy controls ($P < .001$; $\chi^2 = 18.6$; Table I; Fig 2, *A*).

Histamine plasma levels in patients with AE and patients with HIT were significantly elevated compared with control persons ($P < .05$ for AE and $P < .01$ for HIT; Fig 2, *B*). Patients with AE and symptoms of HIT and low diaminoxidase activity had higher histamine levels than patients with AE without HIT, although this did not reach statistical significance. An additional sensitization toward food allergens (hazelnut, peanut, milk, egg, apple, and codfish; $P = .0031$; $\chi^2 = 8.731$) and occurrence of headache ($P = .035$; $\chi^2 = 4.454$) and gastrointestinal symptoms ($P < .0001$; $\chi^2 = 16.6$) could be observed in a significant higher number of patients with AE with low diaminoxidase activity compared with those patients with AE with normal diaminoxidase activity (Table II).

Modified levels of vitamin B_6, copper, or zinc were not associated with reduced diaminoxidase levels in patients with AE

Vitamin B_6 is a postulated cofactor of diaminoxidase,[42] and copper and zinc occupy the active sites in the recombinant enzyme.[9] It has been shown in some studies that a deficiency of vitamin B_6, copper, or zinc might lead to a reduced histamine degradation capacity. To exclude an AE-related malnutrition or deficiency of vitamin B_6, copper, or zinc as a reason for the reduced histamine degradation capacity, we next analyzed the vitamin B_6 plasma and copper and zinc serum levels in parallel to the diaminoxidase activity in a subset of patients with AE (n = 21), patients with HIT without AE (n = 18), and healthy

controls (n = 16). As a result, vitamin B_6, copper, and zinc serum levels were not reduced in patients with AE and did not differ significantly from vitamin B_6, copper, and zinc serum levels in healthy controls or patients with HIT without AE.

Histamine-free diet leads to improvement of symptoms of HIT and SCORAD in patients with AE

To investigate the effect of orally ingested histamine on the clinical status of patients with AE, 17 patients with AE and low diaminoxidase activity with symptoms of HIT were put on a histamine-free diet and given an oral antihistamine once daily. After 2 weeks, a significant improvement of HIT symptoms such as headache, flushing, and gastrointestinal symptoms occurred in most of the patients (Fig 3). Moreover, a significant reduction of both objective and subjective SCORAD was observed (Fig 4). In addition, diaminoxidase activity increased in 3 of 5 patients after the diet, whereas diaminoxidase activity remained unchanged in 2 of 5 patients.

DISCUSSION

Histamine intolerance is caused by a disproportion of the quantity of histamine and the capacity of histamine degradation. This can be a result of histamine overload and/or diaminoxidase deficiency. Exceeding the individual histamine tolerance gives rise to concentration-dependent histamine-mediated symptoms.[43,44] In sensitive patients, symptoms occur even after oral ingestion of small amounts of histamine that are well tolerated by healthy persons. Symptoms can manifest in multiple organs like gastrointestinum, lung, skin, cardiovascular system, and brain according to the expression of histamine receptors.

There are primary and acquired forms of HIT that may result from gastrointestinal diseases,[27,45] competitive inhibition of biogenic acids, or diaminoxidase-blocking drugs.[18,30,46] Elevated histamine concentrations[47] and diminished diaminoxidase activities were found in the colonic mucosa of patients with food allergy (FA).[45,48,49] Furthermore, a low HNMT activity has been observed in both FA[48] and asthma bronchiale.[50]

Here we describe a significantly higher number of symptoms of HIT in a subgroup of patients with AE that might be caused by a reduced histamine degradation capacity in these patients. From the clinical picture, HIT in AE patients represents most of the typical symptoms for classic HIT except for a higher level of drug-induced symptoms of HIT in patients with HIT without AE. Interestingly, most of the patients with classic HIT reporting drug-intolerance related to HIT also had a positive family history for HIT. Together, this might indicate that in a subgroup of patients with HIT, a genetic background, such as functionally relevant single nucleotide polymorphisms in gene regions encoding histamine degrading enzymes, might underlie the reduced histamine degrading capacity.

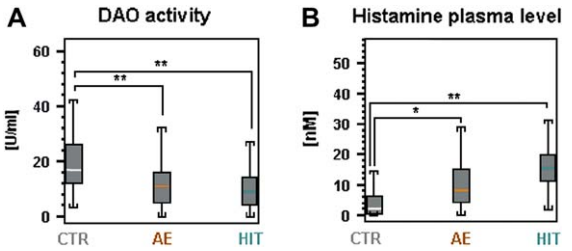

FIG 2. A, Diaminoxidase (DAO) activity in U/mL in serum from patients with suspected HIT, AE, and a healthy control group (*CTR*). SDs are given. $*P < .05$; $**P < .01$. **B,** Histamine levels (normal < 10 nmol/L) are higher in patients with AE and HIT than in controls. SDs are given. $*P < .05$; $**P < .01$.

Polymorphism of the diaminoxidase has been found associated with inflammatory intestinal diseases including FA,[51-53] whereas polymorphism of the HNMT gene associated with low enzyme activity has been reported for patients with asthma.[50,54] Variants of the diaminoxidase or HNMT gene in patients with AE or in primary HIT without inflammatory or allergic diseases have not been investigated yet.

In contrast with the classic HIT, which shows a clear female predominance, symptoms of HIT in patients with AE seem to be independent of the sex of the patient, and no positive family history of HIT was observable. In addition, no differences in serum IgE levels, severity of AE, or the association of rhinitis and asthma between patients with AE with and without HIT could be found (Table II), indicating that AE-associated HIT most likely occurred independently from these parameters. Histamine plasma levels were significantly higher in patients with AE and highest in patients with AE with HIT compared with those without HIT. An additional sensitization toward food allergens could be observed in a significant higher number of patients with AE with low diaminoxidase activity compared with those with normal diaminoxidase activity, supporting the finding that FA can coexist with an impaired histamine degradation capacity,[45] both related to an altered gastrointestinal mucosal barrier.[55,56]

Elevated basal plasma histamine levels[57,58] and increased spontaneous histamine release toward different stimuli[59-61] and after food challenge[55] have been shown in patients with severe AE compared with normal subjects. Reduced type B monoamine oxidase and diaminoxidase activities in AE have been reported in previous studies.[57,62]

Assuming the absence of gastrointestinal diseases or diaminoxidase blocking drugs, an acquired functional impairment of diaminoxidase might be a result of cofactor deficiency or the presence of inhibiting factors. Vitamin B_6 and copper levels, cofactors of diaminoxidase, were normal in our study and previous studies,[42,62] supporting the thesis of diaminoxidase inhibition.

Although elevated histamine concentrations correlated with a high total histamine degradation capacity in colonic biopsies of patients with FA,[63] and diaminoxidase lymph activity in rats was raised after histamine-injection, further histamine administration resulted in comparatively

TABLE II. Comparison of patients with AE with and without low diaminoxidase serum levels and symptoms of HIT*

Group	IgE Serum level, kU/L†	Objective SCORAD†	Subjective SCORAD†	Diepgen score†	Asthma (%)‡	Allergic rhinitis (%)‡	FA (%)‡	Tryptase, μg/L†
AE without HIT (n = 131)	788.07 ± 1018.35	27.79 ± 16.35	34.0 ± 19.96	21.67 ± 5.78	30.53 (n = 40)	66.41 (n = 87)	22.14 (n = 29)	4.82 ± 2.2 (n = 29)
AE with HIT (n = 31)	614.15 ± 923.28	21.587 ± 14.91	27.62 ± 19.439	22.6 ± 5.2561	25.81 (n = 8)	74.19 (n = 23)	48.39 (n = 15)	3.89 ± 1.63 (n = 4)
P value	.367	.056	.114	.538	.604	.404	.003	.483
χ^2					0.269	0.696	8.731	

	Headache‡		Premen-strual headache‡		Flushing‡		Gastro-intestinal symptoms‡		Food intolerance‡		Alcohol intolerance‡		Drug intolerance‡		Urticarial dermo-graphism‡	
Group	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AE without HIT (n = 131)	45	34.35	28	32.56	44	33.59	41	31.3	69	52.57	55	41.98	9	6.87	11	8.4
AE with HIT (n = 31)	17	58.84	6	23.08	12	38.71	22	70.97	15	48.39	17	54.84	2	6.45	3	9.68
P value	.035		.357		.59		<.0001		.667		.195		.934		.82	
χ^2	4.454		0.849		0.291		16.6		0.184		1.677		0.007		0.052	

*For numerical parameters (IgE serum level, objective and subjective SCORAD, and Diepgen Score), means ± SDs are depicted.
†Statistical analysis was performed with the Mann-Whitney *U* Test.
‡Statistical analysis was performed with the χ^2 test.

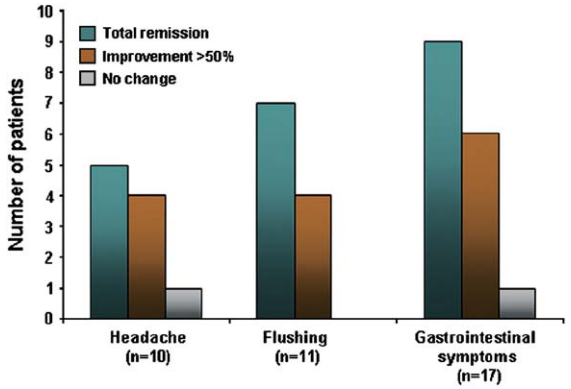

FIG 3. Improvement of symptoms of HIT after 2 weeks of histamine-free diet in patients with AE and HIT and low diaminoxidase activity.

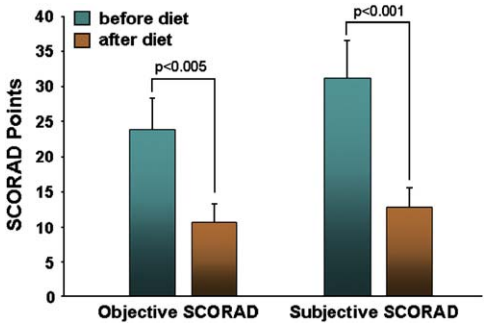

FIG 4. Objective (extent and severity of eczema) and subjective (including pruritus and sleep loss) SCORAD improves in patients with AE and HIT and low diaminoxidase serum levels after 2 weeks of histamine-free diet (n = 17). SCORAD value is depicted on the *x-axis* together with the SEM.

smaller increases, implicating only a limited secretion of diaminoxidase from the intestinal mucosa.[64] In addition, substrate inhibition of recombinant human diaminoxidase has been observed for elevated histamine levels.[9,65] Because the diaminoxidase has also been shown to be inhibited by its degradation product, imidazole acetic acid,[66,67] a negative feedback loop inducing an endogenous inhibition of diaminoxidase caused by high histamine levels might occur in patients with AE. Together, these mechanisms might lead to a generally reduced histamine degradation capacity in patients with AE (Fig 5). However, further investigation of these mechanisms is needed.

Because HIT in patients with AE often occurred in association with food allergy, a careful and detailed anamnestic evaluation of the symptoms and causative factors would be indispensable for the exact diagnosis. Interestingly, a histamine-free diet and antihistamines are capable of improving both HIT-specific and AE-specific symptoms in patients with low diaminoxidase capacity. Omitting orally ingested histamine leads to a regeneration of the diaminoxidase-producing jejunal enterocytes and therefore an increase of enzyme activity, which could also be observed in a subgroup of patients with AE in our study.[32] Supporting the beneficial effect of a histamine-free diet observed in our study, another research group performed a double-blind, placebo-controlled histamine challenge in patients with AE after 2 weeks of a histamine-free diet and reported an aggravation of eczema as well as development of systemic reactions like flush, headache, or dizziness in patients with AE after provocation (Fiedler EM et al, unpublished data, 2005).

From the pathophysiological point of view, 2 different therapeutic strategies for patients with AE and

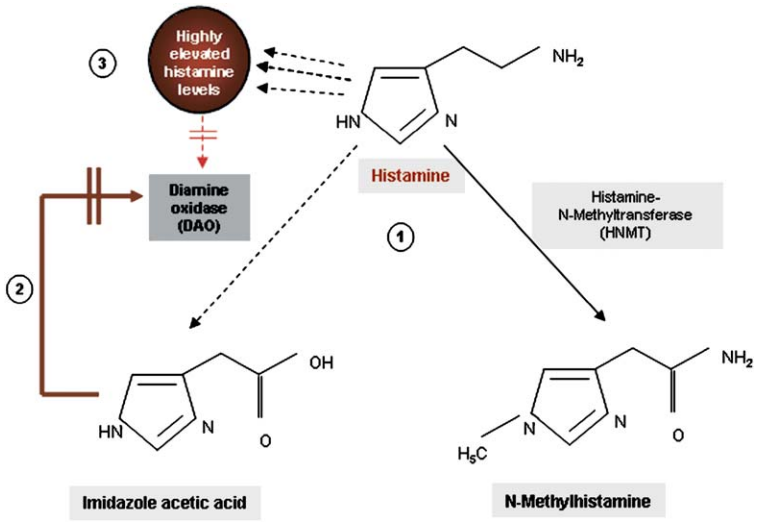

FIG 5. Pathway of histamine degradation. *(1)* Normal histamine degradation pathway by diaminoxidase (DAO) and HNMT. *(2 + 3)* Potential mechanisms responsible for the development of histamine intolerance in patients with AE. *(2)* Enhanced histamine levels might lead to a high histamine degradation mediated by DAO and blockage of DAO by imidazole acetic acid. *(3)* Substrate inhibition on DAO might occur by elevated histamine levels.

AE-associated HIT arise: first, the reduction of the histamine release and histamine levels by a histamine-free diet and antihistamines, and second, the substitution of the enzyme itself or cofactors promoting the activity of diaminoxidase such as vitamin B_6, copper, zinc, or vitamin C in patients with a deficiency on this level. In a recent study, no additional effect could be seen with a histamine-free diet in patients with HIT by add-on medication with antihistamines.[32] Therefore, premedication with antihistamines seems to be advisable only in dietary errors or before exposition to drugs inhibiting diaminoxidase.

In view of our data, we propose that higher histamine plasma levels occurring in AE combined with a reduced histamine degradation capacity might be of relevance for the clinical course of a subgroup of patients with AE. Whether the deficiency in histamine degradation observed in AE results from polymorphisms in the diaminoxidase gene or represents a rather secondary phenomenon, such as an inhibition of diaminoxidase caused by the continuous allergen-induced histamine release in AE, remains to be elucidated.

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